GW26-e4718

Oleanolic Acid Alleviated Pressure-over Load Induced Cardiac remodeling

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OBJECTIVES Previous study has demonstrated that oleanolic acid (OA) possessing the anti-inflammatory and antioxidant properties, blunted high glucose induced diabetic cardiomyopathy, and ameliorated experimental autoimmune myocarditis in mice. However, little is known about its effects on pressure overload induced cardiac remodeling. Herein, we investigated the effect of OA on cardiac remodeling and underlying mechanism.

METHODS Mice, subjected to aortic banding (AB), were randomly assigned into control group and experimental group. OA premixed in diets was administered to mice after 3 days of AB. Echocardiography and catheter-based measurements of hemodynamic parameters were performed after 8 weeks' treatment of OA. Histologic examination and molecular analyses was used to assess cardiac hypertrophy and tissue fibrosis. In addition, we investigated the inhibitory effects of OA on H9c2 cardiomyocytes and cardiac primary fibroblast in vitro.

RESULTS We demonstrated that OA alleviated cardiac remodeling induced by aortic banding (AB), evidenced by heart weight/body weight and lung weight / body weight ratios, echocardiographic and hemodynamic parameters, gene expression of hypertrophic and fibroblastic markers in vivo and vitro. Pressure overload activated the phophorylations of Akt, mTOR, p70s6k, S6, GSK3β and FoxO3a, and treatment of OA attenuated the phophorylation of these proteins.

CONCLUSIONS Our findings suggest that treatment of OA may have a benefit on retarding the progress of cardiac remodeling under long terms of pressure overload. The inhibitory effects of OA on cardiac remodeling may partly involve in the modulated of Akt/mTOR signaling pathway.

GW26-e4739

MaxiK Channel Responsible for Human Macrophage–derived Foam Cell Differentiation via Intracellular Ca2+ Signaling Pathway

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OBJECTIVES The role of MaxiK channels in macrophage immunomodulation has been established. However, it remains unclear whether it is involved in the human macrophage-derived foam cell formation.

METHODS Human peripheral blood monocytes were separated from the platelet-free blood by cell density gradient centrifugation, and then cultured for 5d to differentiate into macrophages. The ratio of cholesterol ester (CE) in the macrophages following intake of oxidized low density lipoprotein (ox-LDL) was analyzed by an enzymatic fluorometric method. The expression level and function of MaxiK channels were investigated using real-time RT-PCR, western blotting, and patch clamp techniques, respectively. The membrane potential was analyzed with the optical mapping of the membrane potential with the voltage-sensitive dyes. Ca^{2+} fluorescence intensity of macrophages was measured by laser confocal microscopy.

RESULTS After the macrophages co-incubated with 30 mg/L ox-LDL at 37°Cfor 60h, the cellular volume obviously enlarged and many red lipid granules were deposited in cytoplasm. The total amount of cholesterol(TC), free cholesterol(FC) and cholesterol ester(CE) in cells markedly increased and the ratio of CE/TC rose from (29.1±3.4)% to (61.1±6.2)% (n=5, $P<0.05$). Meanwhile, MaxiK mRNA and protein expression were 2.4 and 7.27 times higher than those in 5d group ($P<0.05$). However, its current densities did not show a significant difference (36±6 pA/pF *vs* 32.4±6.9 pA/pF, $P>0.05$). Paxilline (1 and 10 μmol/L), the specific blocker of MaxiK channel and inhibiting foam cells formation, at the two doses dose-dependently reduced the macrophage membrane potential over by 30% and 47%, respectively ($P<0.05$). Compared with ox-LDL group, calcium fluorescence intensity of the macrophages decreased by Paxilline (1 and 10 μmol/L) from (766.37±55.10) to (488.32±43.12) and (237.32±24.74), respectively (n=10-15, $P<0.01$).

CONCLUSIONS Although the expression of MaxiK channel is upregulated after differentiating into foam cells, the current densities remains unchanged. It plays a key role in the lipid uptake of macrophage and formation of foam cells via intracellular Ca^{2+} signaling pathway.

GW26-e5327

Micro-calcification Regression in ApoE-/- Mice Spontaneous Atherosclerotic Plaque by Simvastatin on Inhibition of Endoplasmic Reticulum Mediated Apoptosis

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OBJECTIVES To investigate the effect of simvastatin on atherosclerotic micro-calcification and its endoplasmic reticulum mediated apoptosis pathway.

METHODS 24 male ApoE-/- mice on a C57BL/6J genetic background and 12 male C57BL/6J mice were selected when they were 8-week-old. 24 male ApoE-/- mice were randomly divided into model group and simvastatin group (n=12 per group). 12 male C57BL/6J mice were regarded as control group. After receiving adaptive feeding in the animal center for two weeks, all mice were treated with intragastric administration, and model group and simvastatin group were feed with a high-fat diet. Control group and model group received 0.2ml PBS buffer per day for 8 weeks; Simvastatin group received simvastatin (20mg/kg dissolved in 0.2ml PBS buffer for intragastric administration) every day for 8 weeks. The body weight of mice were recorded every day during the whole experiment. They were sacrificed and their aorta and aortic sinus were separated. The aorta of mice were stained with oil red O and aortic sinus paraffin sections were processed with HE, Von kossa, TUNEL and immunohistochemical staining to observe plaque size, atherosclerotic micro-calcification, apoptosis and expression of related endoplasmic reticulum pathway proteins.

RESULTS Compared to model group, simvastatin group was not statistically significant ($P> 0.05$). Serum lipid parameters of TG, TC, LDL-C, HDL-C in the model group were significantly higher, compared with control group and model group ($P <0.01$). HDL-C/LDL-C value of simvastatin group was 0.17 ± 0.005, which represented a slight increase compared with model group (0.15 ± 0.003), but the difference was not statistically significant ($P = 0.09$). Percentage of aortic plaque area of model group and simvastatin group were (54.50 ± 15.41)% and (33.69 ± 9.72)%,which simvastatin group significantly reduced ($P <0.05$). And the mean plaque area of aortic sinus of simvastatin group was significantly less than model group ($P <0.05$). No calcification was found in control group. In addition, percentage of micro-calcification area of simvastatin group (2.33 ± 0.73)% was lower than model group (10.87 ± 2.41)% ($P <0.05$). A certain apoptosis was observed in each group. Apoptosis rate of control group was (30.90 ± 1.75)%, model group (66.43 ± 4.05)% and simvastatin group (47.01 ± 5.94)%, respectively. Apoptosis rate of model group was significantly higher than control group ($P <0.01$). And it was significantly reduced in simvastatin group compared with the model group ($P <0.05$). Protein expressions in aortic sinus of the three groups of GRP78, CHOP and Caspase12 were observed in varying degrees. The highest expression levels of the three proteins were observed in model group, which were significantly decreased in simvastatin group.

CONCLUSIONS Simvastatin may reduce endoplasmic reticulum stress-mediated apoptosis involved regression of atherosclerotic micro-calcification.

GW26-e0405

The applied research of C-phycocyanin from spirulina platensis on the targeted therapy of CD59 gene in atherosclerotic mice

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OBJECTIVES To study the effects of C-phycocyanin on occurrence and development of atherosclerosis, and research the regulatory effects of CD59 gene on anti-atherosclerosis of C-phycocyanin(C-PC).

METHODS 80 mice with ApoE gene deletion (ApoE(-/-)) were randomly divided into five groups: control group, CD59siRNA